

Statement of Vision from the Center's Director Professor Kohji Nishida, Osaka University

Conquering disease is an ambitious goal that has persisted throughout human history. To achieve this goal, we will establish a WPI center that will create a completely new scientific field, Human Metaverse Medicine, which will bring digital transformation to medicine.

Medical breakthroughs in the 20th century were largely achieved via animal experimentation. In the early 1970s, life sciences research blossomed, joining biology and medicine, and promising the means to conquer cancer and other diseases. A reductive approach, centered on the concept of a discrete dichotomy between health and disease has been routinely employed to study illness. Though many diseases with clear cause and effect have been defeated using this approach, and life expectancy has been significantly extended, other **diseases with complex pathologies remain resistant** to these efforts. For these, **no preventive or curative treatments exist**. In addition, an explosion in prevalence of common diseases has occurred, including diabetes, dementia, and heart failure. These are influenced by **the deterioration of homeostasis brought on by aging** (a process that varies greatly among individuals). **Interactions between genes and environmental factors** also compound metabolic differences and organ abnormalities. For these diseases, the conventional dichotomy between health and disease is lacking. In contrast, new medical research, based on the concept of a continuum between health and disease, as well as the notion of pre-symptomatic pathological states, or "Mibyo", has emerged. These efforts rely on mathematical methods, such as artificial intelligence (AI) and computer modeling, and real-world data and disease specimens from patients.

This proposal will take a new, nuanced approach to disease, by creating an academic system to comprehensively and continuously understand the process of homeostatic disruption that occurs in each individual human body. We will revolutionize this field by creating a World Premier International (WPI) Research Center, the "**Premium Research Institute for Human Metaverse Medicine (PRIMe)**". PRIMe will promote a paradigm shift by integrating organoid-based biomedical science research with the information and mathematical sciences, quantum science, clinical medicine, and the humanities and social sciences. We define the "human metaverse" as an information space platform for sharing and utilizing ***in silico* patient-specific models constructed from human data, or "biodigital twins"**. Through our interdisciplinary research (**Fig. 1**), **we will create the scientific field of "human metaverse medicine,"** which will elucidate disease mechanisms and pre-disease pathological states. This new analytical platform will aid in development of personalized disease prevention methods and curative treatments and generate predictive methods for disease onset and drug response that are optimized to the individual. Furthermore, **we will construct an information space platform—the human metaverse** itself—to enable researchers and medical professionals around the world to share and utilize information in the form of human-biodigital twins. We will work with academics in the humanities and social sciences to interrogate relevant **ethical, legal, and social issues (ELSI)** throughout the process; any issues that arise will be collaboratively solved with key stakeholders.

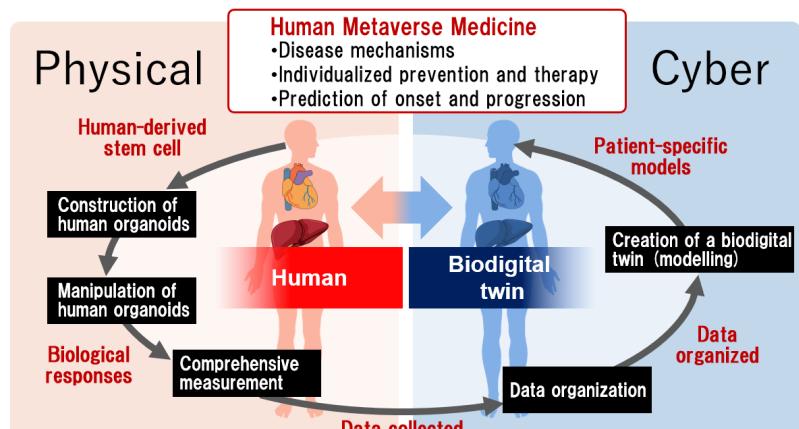


Figure 1: Creation of the "Human Metaverse Medicine"

To accomplish this goal, we will create **banks of organoids from human-derived stem cells**. Organoids are miniature three-dimensional tissue constructs that reflect the individual human source and

mimic human organs. Organoids, constructed from normal, pre-symptomatic or diseased patients, will be used to measure responses to perturbation by genetic and environmental factors at the molecular, cellular, tissue, organ, multiorgan, and multisystem levels, in multiple dimensions and layers, by using **advanced measurement techniques**. By integrating, organizing and analyzing these data, along with published population health and disease datasets, using artificial intelligence (AI)-based machine learning and mathematical modeling, etc., **we will model the continuum from homeostatic disruption to phenotypic manifestation of disease. The resulting model will, in essence, be a human biogigital twin, lodged in a cyber space. As our first content area, we will focus on development, reproduction, and aging**, aiming to discover common, as well as unique, principles that lead to the onset of disease at each time.

The goals of this initiative are threefold: **1) creation of "human metaverse medicine" to comprehensively understand disease, 2) construction and social implementation of a "human metaverse" to prevent and treat disease, and 3) development of the next generation of researchers** trained in the new approaches we propose. In addition, we will foster early career researchers who can navigate "human metaverse medicine" as a whole and develop it widely on the international stage. To realize this goal, we will conduct interdisciplinary research "under-one-roof" in an interactive physical environment highly attuned to cooperation, collaboration, and collegiality. **A doctoral human metaverse medicine educational program will be established** at the graduate school. Human metaverse science will be included in the Cross-Disciplinary Graduate Programs and Challenging Research Programs for Next-Generation Researchers

We will assemble outstanding researchers from Osaka University to work with new recruits from overseas to establish a research system that fuses these diverse disciplines. Center Director, Kohji Nishida, has extensive experience leading large projects to success, and has published widely in the fields of fundamental stem cell science and organoid research (e.g., Nature 2016, 2022) and applied clinical research (e.g., New Engl J Med 2004). I will certainly draw on my vision to create exceptional value in the new WPI venture. PRIME will have two Deputy Directors: Takanori Takebe, Deputy Director of the Organoid Center at Cincinnati Children's Hospital since 2017, a leading international institution for organoid research (e.g., Nature 2013, 2017, 2019, Nat Med 2020) and Mariko Okada (e.g., Cell 2010, Science 2014, 2021, Cell Rep 2020), a leader in the fusion of research between informatics and biology in Japan. PRIME principal investigators (PIs) will be selected through interview, including seven experts in the field of organoid-based biomedical science, ten in information and mathematical sciences (including three at satellite institutes), two in quantum science, and one in ELSI (in total twenty PIs including four female PIs). Equity, diversity, and inclusion will be closely considered during recruitment. Satellite centers will be established at **the RIKEN Center for Advanced Photonics** and **the Bio-Medical Informatics Research Center at NTT Basic Research Laboratories**. In addition, **four overseas research institutes** renowned for their research in organoids and information and mathematical sciences will be invited as collaborating institutions. PIs or visiting professors will be invited to the new WPI Research Center to develop an international research environment and expand human metaverse disease science internationally through the collaborating institutions.

It is the shared dream of humankind to live a long and healthy life. PRIME will contribute to the realization of this dream by achieving an unparalleled fusion of human biomedical sciences, information and mathematical sciences, quantum science, clinical medicine, and the humanities and social sciences. PRIME will enable many unsolved diseases to be understood and fought in new ways. By spreading our results throughout the world, we will make new and unique contributions to a healthy and sustainable society for all people.